# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**40032**

# BIOEQUIVALENCY REVIEW(S)

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

ANDA # 40-032 SPONSOR : Roxane Laboratories
DRUG & DOSAGE FORM : Cyclophosphamide Tablets
STRENGTHS : 25 mg, and 50 mg
TYPES OF STUDIES: One BE study on the 50 mg strength,
Dissolution testings on both strengths, and
Waiver for the 25 mg strength.
CLINICAL STUDY SITE:
ANALYTICAL SITE :

SUMMARY:

Fasting BE study on the 500 mg strength: Acceptable
Limited food study on the 500 mg strength: Acceptable
Dissolution testings on both strengths: Acceptable
Waiver request for the 250 mg strength: Granted

PRIMARY REVIEWER :Lin-Whei Chuang BRANCH : I

INITIAL : /S/ DATE : 9/9/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : /S/ DATE : 9/7/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE : Dale Conner, PharmD.

INITIAL : /S/ DATE : 9/9/98

**Cyclophosphamide**
**Tablet, 25 mg and 50 mg**
**ANDA # 40-032**
**Reviewer: L. Chuang**

**Roxane Laboratories, Inc.**
**Columbus, Ohio**
**Submission Date:**
**April 3, 1998**
**September 3, 1998**
August 10, 1998

## Review of a New Bioequivalence Study (Amendment to an Unacceptable Bioequivalence Study)

The bioequivalence study presented in the original application submitted on 12/13/93 was found to be incomplete by the Division on 03/09/94 due to 7 deficiencies (see attached review). The subsequent amendment submitted by the sponsor on 07/12/94 was found to be unacceptable by the Division on 03/13/95 (see attached review).

The sponsor has conducted a new bioequivalence study according to the protocol submitted on 1/8/96 and reviewed on 6/3/96 (see attached). Results of the study are reviewed below:

### Bioequivalence Study:

Clinical Results:

The protocol of the study was dated 1/4/96 with revisions on 9/25/96 and 11/11/96 and amendment on 3/13/97. The C.R.O. of the study was Approval dates of the protocol by various IRBs at different clinical sites are listed below:

| Site # | Investigator | IRB | Approval date |
|---|---|---|---|
| 2 | | | 4/24/97 |
| 4 | | | 6/4/97 |
| 5 | | | 2/22/96 (site closed, amendment was not sent) |
| 6 | | | 4/15/97 |
| 8 | | | 3/4/97 |

| | | |
|---|---|---|
| 8 | | 3/4/97 |
| 9 | | 4/29/97 |
| 10 | | 4/17/97 |
| 11 | | 7/16/97 |
| 15 | | 7/7/97 |

Clinical studies were conducted during 12/20/96-10/20/97 (date of 14th day). Analytical study was conducted at during 1/6-21/98.

A total of 32 patients (14 Caucasian, 11 Black, 5 Hispanic, 1 Spanish and 1 American-Indian) entered the trial at 9 clinical centers (under 9 different investigators) and were assigned to one of the following treatments for 7 days and cross over to the other treatment the next 7 days:

Treatment A: Test drug -- Cyclophosphamide 50 mg tablets, 100 mg/m$^2$ (3 or 4 tablets), manufactured by Roxane Laboratories (lot #969064, lot size tablets, potency %), manufactured 8/96, once a day for 7 days.

Treatment B: Reference drug -- Cytoxan 50 mg tablets, 100 mg/m$^2$, (3 or 4 tablets) manufactured by Bristol-Myers Squibb (lot #MH016, potency %, expires 9/99), once a day for 7 days.

Patients were on the chemotherapy regimen of either CMF or CAF (see attached review of the protocol).

Some patients received alternating doses of 150 and 200 mg daily (subjects #53, 54, 55). The second treatment regimen for these patients was of 6-day duration in order to assure the same dose level on the pharmacokinetic sampling days. They were grouped according to the dose they had received on the day of blood sample

collection. Each patient received identical dose level of test and reference products.

Treatment sequence assignment among 32 patients were:

Sequence AB: subjects #5, 13, 14, 21, 23, 30, 31, 34, 40, 42, 43, 54, 55, 57, 58, 69
Sequence BA: subjects #1, 15, 16, 17, 22, 24, 29, 32, 33, 37, 38, 39, 41, 44, 53, 70

Investigator assignment were:

Investigator #2: subject #5
Investigator #4: subjects #13, 14, 15, 16, 57, 58
Investigator #5: subjects #17
Investigator #6: subjects #21, 22, 23, 24
Investigator #8: subjects #29, 30, 31, 32
Investigator #9: subjects #33, 34
Investigator #10: subjects #37, 38, 39, 40, 53, 54, 55
Investigator #11: subjects #1, 41, 42, 43, 44
Investigator #15: subjects #69, 70

Regimen assignment were:

CMF: subjects #5, 13, 14, 17, 21, 22, 23, 24, 29, 33, 34, 37, 38, 39, 41, 53, 54
CAF: subjects #1, 15, 16, 30, 31, 32, 40, 42, 43, 44, 55, 57, 58, 69, 70

On days 7 and 14, a pre-dose blood sample was drawn prior to the administration of cyclophosphamide. Patients had standard breakfasts (consisted of decaffeinated tea/decaffeinated coffee, buttered toast and cereals, specifically no citrus fruit or citrus fruit products were allowed) before pharmacokinetic blood samplings were conducted at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, & 24 hours post-dose. Serum samples were frozen at -15°C until being transferred to and stored at -20°C and analyzed for cyclophosphamide concentrations.

Among the 32 patients enrolled, 31 completed both periods and 25 patients were evaluable. Subject #22 had to withdraw from the study on day 5 due to personal reason. The pharmacokinetic parameters of subjects #34 were not possible to analyze due to insufficient number of serum cyclophosphamide concentrations above the 0.01 ug/mL quantitation limit. Subjects #16, 38, and 39 had different doses of cyclophosphamide on the two blood sampling days. Subject #69 had reference drug on both blood sampling days, and subject #70 had test product on both blood sampling days.

A total of 71 adverse events were reported by 23 patients; 36 during treatment A by 14 patients, 34 during treatment B by 17 patients, and a case of dysphagia reported by #17 but the starting date was not recorded. "Nausea" and other symptoms of the digestive system were the most frequent events, others involved hemic and lymphatic, metabolic and nutritional, musculoskeletal, nervous, respiratory, skin and appendages, special sense and urogenital systems.

Comments on the clinical Results:

1. Clinical results show no major protocol deviation.
2. Adverse events occurred with almost identical frequency during both treatment.
3. In the original bioequivalence study submitted on 12/13/93, cyclophosphamide was administered under fasting condition on days 7 and 14 and patients continued to fast until 2-hour post-dose. In the present study, however, patients were given standard breakfast on days 7 and 14 before pharmacokinetic blood sampling. This is acceptable considering that nausea and vomiting commonly occur with cyclophosphamide therapy (PDR, 1996).
4. Clinical results are acceptable.

Analytical Method --

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commercial

information

analytical method

Pharmacokinetic and Statistical Results:

Out of the 650 serum samples from the 25 evaluable subjects, the firm noted that only 1 sample had analytical failure and the serum cyclophosphamide concentration of this sample was not reportable (subject #30, period 1, treatment A, hour 24). However, there are 25 missing data points for these 25 evaluable subjects, 10 of them were adjacent to the estimated Cmax of subjects #30, 31, 42, 55 (treatment A) and subjects #1, 33, 41, 42, 43, 55 (treatment B). All these missing data points were due to analytical failure and insufficient amount of plasma sample for re-assay (see submission of 9/3/98).

Using data from the 25 evaluable subjects submitted by the firm, the reviewer calculated the mean plasma concentrations of cyclophosphamide at each sampling point on day 7 or 14, after both treatments and the mean pharmacokinetic parameters are presented in Figure 1 and Tables 3&4. The dosage (received on both blood-collection days) distribution among the 25 evaluable patients were:

150 mg/day: subjects #1, 13, 14, 21, 23, 29, 30, 32, 33, 37, 41, 43, 44, 54, 58
200 mg/day: subjects # 5, 15, 17, 24, 31, 40, 42, 53, 55, 57

**Table 3: ARITHMETIC MEANS OF SERUM CYCLOPHOSPHAMIDE LEVELS (UG/ML) AND RATIOS OF MEANS --3X50 MG IN 10 SUBJECTS AND 4X50 MG IN 15 SUBJECTS UNDER FED CONDITIONS--- (N=25 EXCEPT WHEN INDICATED)**

| | MEAN-TEST | SD | MEAN-REF. | SD | RATIO T/R |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.594 | 0.439 | 0.555 | 0.660 | 1.070 |
| 0.5 | 1.853* | 1.777 | 1.155 | 1.685 | 1.605 |
| 1 | 3.189* | 2.015 | 2.241 | 1.918 | 1.423 |
| 1.5 | 3.495** | 1.290 | 3.010** | 1.725 | 1.161 |
| 2 | 3.605* | 0.620 | 3.469* | 1.237 | 1.039 |
| 2.5 | 3.692 | 0.731 | 3.859**** | 0.855 | 0.957 |
| 3 | 3.521 | 0.681 | 3.650** | 1.067 | 0.965 |
| 4 | 3.193* | 0.667 | 3.280** | 0.724 | 0.973 |
| 6 | 2.484 | 0.579 | 2.603 | 0.624 | 0.954 |
| 8 | 1.935 | 0.506 | 2.122* | 0.531 | 0.912 |
| 10 | 1.542* | 0.474 | 1.611 | 0.504 | 0.957 |
| 12 | 1.195** | 0.323 | 1.303 | 0.512 | 0.918 |
| 24 | 0.412* | 0.471 | 0.331*** | 0.188 | 1.245 |

* = (N=24), ** = (N=23), *** = (N=22), **** = (N=21)

**TABLE 4: ARITHMETIC MEANS OF CYCLOPHOSPHAMIDE PHARMACOKINETIC PARAMETERS AND RATIOS OF MEANS --3X50 MG IN 10 SUBJECTS AND 4X50 MG IN 15 SUBJECTS UNDER FED CONDITIONS--- (N=25)**

| | MEAN-TEST | SD | MEAN-REF. | SD | RATIO T/R |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 45.763 | 26.258 | 41.775 | 13.837 | 1.095 |

| | | | | | |
|---|---|---|---|---|---|
| AUCT | 38.396 | 10.509 | 37.175 | 11.047 | 1.033 |
| CMAX | 4.419 | 0.926 | 4.327 | 0.775 | 1.021 |
| KE | 0.118 | 0.040 | 0.118 | 0.020 | 1.002 |
| LAUCI | 42.122 | --- | 40.086 | --- | 1.051 |
| LAUCT | 37.219 | --- | 35.945 | --- | 1.035 |
| LCMAX | 4.327 | --- | 4.267 | --- | 1.014 |
| THALF | 7.208 | 5.149 | 5.688 | 1.588 | 1.267 |
| TMAX | 1.757 | 0.862 | 2.232 | 1.001 | 0.787 |

The ratios of test to reference products of 3 major pharmacokinetic parameters of cyclophosphamide are presented in Table 5.

**TABLE 5: RATIOS OF TEST TO REFERENCE PRODUCTS**
**--3X50 MG IN 10 SUBJECTS AND 4X50 MG IN 15 SUBJECTS UNDER FED CONDITIONS---**

| SUB | SEQ | AUCT | AUCI | CMAX |
|---|---|---|---|---|
| 1 | 2 | 1.26 | 1.24 | 1.37 |
| 5 | 1 | 1.28 | 1.27 | 1.45 |
| 13 | 1 | 0.65 | 0.61 | 0.72 |
| 14 | 1 | 1.00 | 0.98 | 1.01 |
| 15 | 2 | 1.01 | 0.98 | 1.58 |
| 17 | 2 | 0.98 | 1.00 | 0.92 |
| 21 | 1 | 0.86 | 0.86 | 0.78 |
| 23 | 1 | 1.22 | 1.21 | 1.20 |
| 24 | 2 | 1.01 | 1.04 | 0.88 |
| 29 | 2 | 0.98 | 0.99 | 1.05 |
| 30 | 1 | 1.12 | 0.93 | 1.17 |
| 31 | 1 | 0.68 | 1.20 | 0.56 |
| 32 | 2 | 1.58 | 3.32 | 1.03 |
| 33 | 2 | 1.12 | 1.17 | 1.21 |
| 37 | 2 | 1.11 | 1.13 | 1.09 |
| 40 | 1 | 1.02 | 0.99 | 1.05 |
| 41 | 2 | 0.99 | 1.05 | 1.13 |
| 42 | 1 | 1.53 | 1.30 | 1.14 |
| 43 | 1 | 0.97 | 0.60 | 0.89 |
| 44 | 2 | 1.05 | 1.08 | 0.74 |
| 53 | 2 | 0.98 | 0.97 | 0.89 |
| 54 | 1 | 1.00 | 0.98 | 1.01 |
| 55 | 1 | 0.98 | 0.95 | 1.14 |
| 57 | 1 | 1.05 | 1.00 | 0.99 |
| 58 | 1 | 0.91 | 0.90 | 1.00 |
| MEAN | | 1.05 | 1.11 | 1.04 |
| N | | 25 | 25 | 25 |
| MINIMUM | | 0.65 | 0.60 | 0.56 |
| MAXIMUM | | 1.58 | 3.32 | 1.58 |

The mean ratio of AUCT/AUCI was 0.90 (0.44-0.99) during treatment A and 0.90 (0.58-0.98) during treatment B. The ratios of AUCT/AUCI for subjects #31 & 32 (treatment A) and subjects #30, 42, &43 (treatment B) were <0.8.

Since this was a study conducted in 9 clinical centers with 9 investigators in patients under 2 different chemotherapy regimens and given 2 different doses of cyclophosphamide, ANOVA was performed on the untransformed and log-transformed data of AUCT,

AUCI and CMAX using a SAS GLM model including factors of DOSE, INV, REG, SEQ, SUB(SEQ*DOS*INV*REG), PER, TRT, TRT*DOSE, TRT*INV, and TRT*REG. The sequence effect was tested using the subjects within sequence effect as the error term with a 10% level of significance. The treatment and period effect were tested against the residual mean square error with a level of significance of 5%. Results showed no significant interactions ($p<0.05$) of any factors involving dose, investigator or regimen.

ANOVA was then re-conducted without these factors. No significant treatment or sequence effect were detected for any of the pharmacokinetic parameters. The least square means, 90% confidence intervals, and ratios of means are presented below in Table 6.

**TABLE 6: LS MEANS (LSM) AND 90% CONFIDENCE INTERVALS (CI) of CYCLOPHOSPHAMIDE --3X50 MG IN 10 SUBJECTS AND 4X50 MG IN 15 SUBJECTS UNDER FED CONDITIONS---**

| PARAMETER | TEST LSM | REF.LSM | RATIO T/R | 90% CI |
|---|---|---|---|---|
| AUCI | 46.337 | 41.456 | 1.118 | 91.464 - 132.081 |
| AUCT | 38.572 | 37.069 | 1.041 | 95.143 - 112.965 |
| CMAX | 4.444 | 4.329 | 1.027 | 94.477 - 110.837 |
| LAUCI | 42.356 | 39.822 | 1.064 | 96.159 - 117.650 |
| LAUCT | 37.354 | 35.886 | 1.041 | 97.259 - 111.401 |
| LCMAX | 4.351 | 4.271 | 1.019 | 94.082 - 110.287 |

The firm stated the 4 patients (subjects 5, 23, 30 and 32) had large inconsistencies in their dosing intervals between the 2 treatments and excluded them from the re-analysis of statistics. Results of the re-analysis indicated that the 90% confidence intervals of LNAUCT and LNCmax were both within the acceptable range of 80-125%.

Comments:

1. All ANOVA analysis and computation of pharmacokinetic parameters and 90% confidence intervals have been confirmed by the reviewer (only the values of AUCI varied slightly from those submitted by the firm). The 90% confidence intervals of LNAUCT, LNAUCI and LNCmax were all within the acceptable range of %.

2. It was noted that there are 10 missing data points for the 25 evaluable subjects that were adjacent to the estimated Cmax of

subjects #30, 31, 42, 55 (treatment A) and subjects #1, 33, 41, 42, 43, 55 (treatment B). Therefore, the reviewer re-conducted statistical analysis excluding these subjects and the 4 subjects who had large inconsistencies in their dosing intervals between the 2 treatments (subjects #5, 23, 30 and 32). Results of these re-analysis present below in Table 7 indicate that all 90% confidence intervals are within the acceptable range of %.

**TABLE 7: LS MEANS (LSM) AND 90% CONFIDENCE INTERVALS (CI) of CYCLOPHOSPHAMIDE 3 OR 4X50 MG UNDER FED CONDITIONS -- (N = 14)**

| PARAMETER | TEST LSM | REF.LSM | RATIO T/R | 90% CI |
|---|---|---|---|---|
| AUCI | 38.708 | 41.502 | 0.933 | 82.994 - 103.540 |
| AUCT | 36.067 | 38.200 | 0.944 | 85.142 - 103.691 |
| CMAX | 4.318 | 4.470 | 0.966 | 86.039 - 107.138 |
| LAUCI | 37.585 | 39.287 | 0.957 | 89.936 - 101.769 |
| LAUCT | 35.289 | 36.527 | 0.966 | 91.062 - 102.499 |
| LCMAX | 4.227 | 4.401 | 0.960 | 87.302 - 105.655 |

## Dissolution Data

The firm submitted the following comparative dissolution data:

**Table 8 - In Vitro Dissolution Testing**

Drug (Generic Name): Cyclophosphamide
Dosage Form: Tablet
Dose Strength: 25 and 50 mg
ANDA No.: 40-032
Firm: Roxane Laboratories, Inc.
Submission Date: 4/3/98

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Basket RPM: 100 No. Units Tested: 12
Medium: Water Volume: 900 mL
Tolerance: NLT % in 45 minutes
Reference Drug: Cytoxan® tablets (Bristol-Myers)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

| Sampling Times (minute) | Test Product Lot # 979049 Strength (mg): 25 | Reference Product Lot # MK018 Strength (mg): 25 |
|---|---|---|

| | Mean % | Range | %CV | Mean % | Range | %CV |
|---|---|---|---|---|---|---|
| 15 | 90 | | 21 | 85 | | 18 |
| 30 | 101 | | 2 | 101 | | 3 |
| 45 | 101 | | 3 | 101 | | 4 |
| Sampling Times (minute) | Test Product Lot # 969064 Strength (mg): 50 | | | Reference Product Lot # MH016 Strength (mg): 50 | | |
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 99 | | 5 | 80 | | 24 |
| 30 | 100 | | 3 | 99 | | 2 |
| 45 | 100 | | 3 | 99 | | 3 |

Comments:

The dissolution data submitted by the firm are acceptable per Agency's letter of 3/9/92 and *"Handbook of Drug Dissolution Standards"*. The current USP 23 does not contain information on the dissolution test of cyclophosphamide tablets.

**Formulations of Roxane's Cyclophosphamide Tablets**
**-- Not Releasable through FOI --**

| | 25 mg tablet | 50 mg tablet |
|---|---|---|
| **Ingredient** | Amount/tablet | Amount/ Tablet |
| **Core Tablet** | | |
| Cyclophosphamide Monohydrate | mg* | mg* |
| Microcrystalline Cellulose (Avicel PH101) | mg | mg |
| Lactose | mg | mg |
| Magnesium Stearate | mg | mg |
| Total Core Tablet Weight | mg | mg |
| **Coat Tablet** | | |

| | | |
|---|---|---|
| Acacia | mg | mg |
| Microcrystalline Cellulose (Avicel PH101) | mg | mg |
| Microcrystalline Cellulose (Avicel PH102) | mg | mg |
| FD and C Blue #1 | mg | mg |
| Lactose | mg | mg |
| Magnesium Stearate | mg | mg |
| Total Coat Tablet Weight | mg | mg |
| Compressed Coated Tablet Weight | mg | mg |

Comment:

The formulations of the two strengths of the test product are proportionally identical.

**Waiver Request:**

Although the submission does not contain a request of waiver for the firm's 25 mg tablets, a waiver of *in vivo* bioequivalence study requirements can be granted per 21 CFR Section 320.22(d)(2).

**Recommendation:**

1. The bioequivalence study conducted by Roxane Laboratories, Inc. on its Cyclophosphamide 50 mg tablet, lot #969064 compared to Cytoxan[R] 50 mg tablet, lot #MH016, manufactured by Bristol Myers Co., has been found acceptable by the Division of Bioequivalence.

3. The dissolution testings conducted by Roxane Laboratories, Inc. on its Cyclophosphamide 50 mg tablet, lot #969064 compared to Cytoxan[R] 50 mg tablet, lot #MH016, manufactured by Bristol Myers Co., has been found acceptable by the Division of Bioequivalence. The dissolution testing should be

incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of water at 37° C using USP 23 apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

> *"Not less than % (Q) of the labeled amount of cyclophosphamide in the dosage form is dissolved in 45 minutes."*

3. The waiver of bioequivalence requirement for the firm's cyclophosphamide 25 mg tablets can be granted per 21 CFR 320.22(d)(2).

/S/ 9/9/98

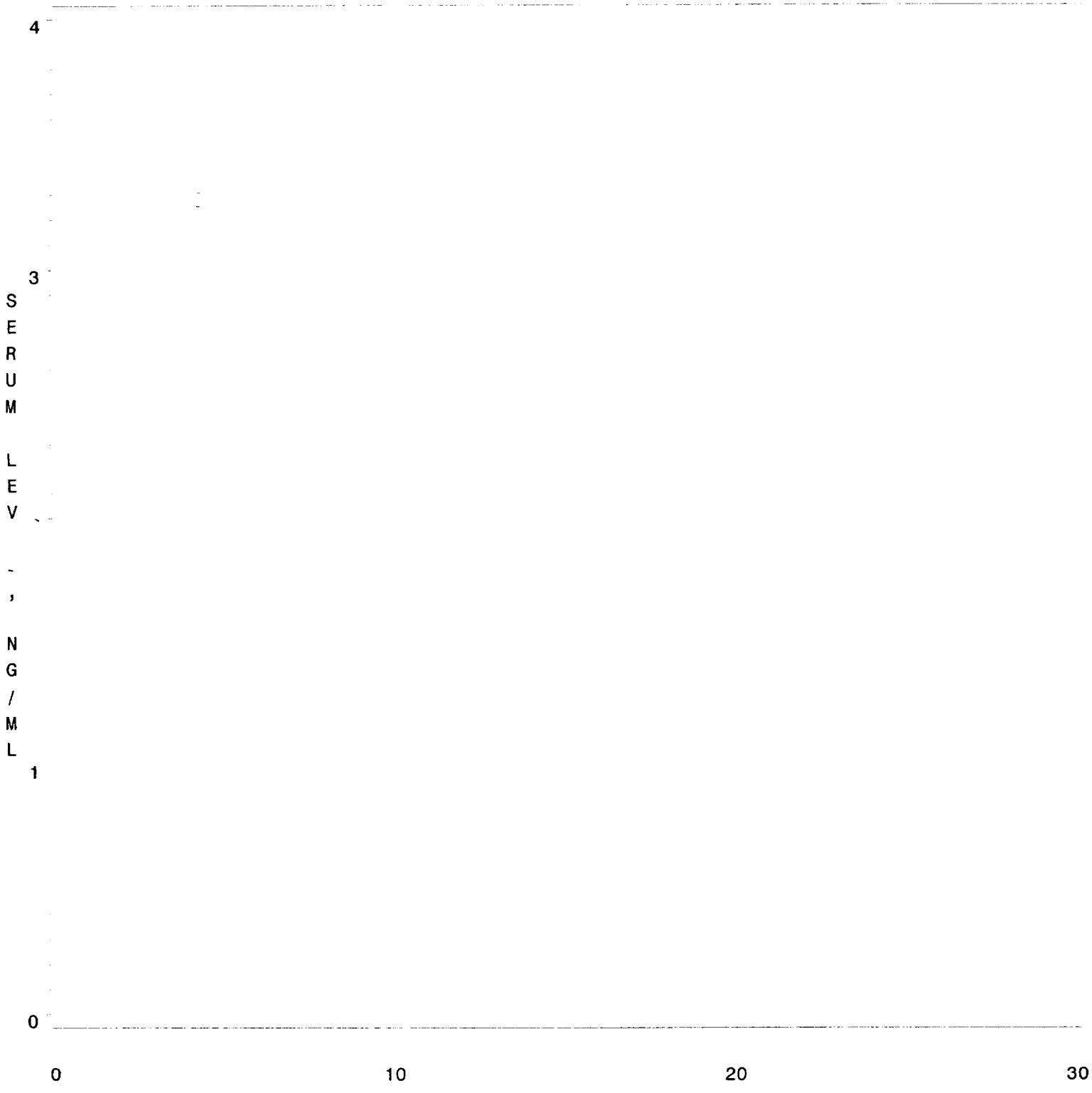
Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG /S/ for Y Huang 9/9/98
FT INITIALLED YHUANG

Concur /S/ Date: 9/9/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

# FIG 1. SERUM CYCLOPHOSPHAMIDE LEVELS

CYCLOPHOSPHAMIDE TABLETS, 50 MG, ANDA #40-032
UNDER FED CONDITIONS
DOSE=3 OR 4 X 50 MG




1=TEST(ROXANE) 2=REF(BRITOL MYERS)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-032 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Cyclophosphamide Tablets, 25 mg and 50 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37° C using USP Apparatus 1 at 100 rpm. The test product should meet the following specifications:
>
> Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 3 1996

Cyclophosphamide
Tablet, 50 mg
ANDA # 40-032
Reviewer: L. Chuang

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
January 8, 1996

## Review of a Protocol of a Bioequivalence Study

The bioequivalence study presented in the original application submitted on 12/13/93 was found to be incomplete by the Division on 03/09/94 due to 7 deficiencies (see attached review). The subsequent amendment submitted by the sponsor on 07/12/94 was found to be unacceptable by the Division on 03/13/95 (see attached review).

The sponsor will conduct a new bioequivalence study according to the protocol in this submission. The only major difference between the old study and the new proposed study is the dosage of the drug. In this new study the daily dose will be limited to 3-4 tablets (150-200 mg) instead the 1-4 tablets (50-200 mg) used in the old study.

The objective of this study is to evaluate the bioequivalence of the test product and the reference drug, Cytoxan$^R$ 50 mg tablet manufactured by Bristol Myers Co..

The design is an open label, 2-way crossover study. Each patient will be randomized to receive the test product or the reference drug for the first 7 days and switch product for the following 7 days. A total of 32 patients are expected to enroll in up to 8 centers to achieve 24 evaluable patients.

The C.R.O. of the study is . The protocol was dated 01/04/96.

The inclusion criteria are:

1. Females, 18-69 years old, negative pregnancy test, willingness to provide written informed consent.
2. Patients receiving one of the following chemotherapy regimen for treatment of primary tumor in breast cancer:

   * CMF
     Cyclophosphamide 100 mg/m$^2$/day P.O., Day 1 through 14
     Methotrexate 30-40 mg/m$^2$ IV, Days 1, 8, q 21-28 days
     5-FU 400-600 mg/m$^2$IV, days 1, 8, q 21-28 days

   * CAF
     Cyclophosphamide 100 mg/m$^2$/day P.O., Day 1 through 14
     Adriamycin (Doxorubicin) 60-75 mg/m$^2$ , single IV injection, q 21-28 days

5-FU 400-600 mg/m$^2$IV, days 1, 8, q 21-28 days

3. Patients who had undergone modified radical mastectomy, segmental mastectomy, lumpectomy, or partial mastectomy and receiving post-operative adjuvant chemotherapy are eligible.
4. Patients diagnosed with metastasis which will not, in the investigator's opinion, affect metabolism and absorption.
5. Patients who have been previously treated with IV cyclophosphamide must have been benefitted from treatment with oral cyclophosphamide for at least 1 cycle prior to entry to this study.
6. patients who do not have clinically significant abnormal laboratory values which would compromise patient safety or unable to be treated with cyclophosphamide.
7. patients must weigh 100-220 lb, individual weight should be 80-140% of normal for height and body frame.
8. Patients should require 150-200 mg of cyclophosphamide daily.
9. Concurrent tamoxifen is allowed provided patients have been on tamoxifen for at least 14 days and the dose remains constant during the entire course of the study.

The Exclusion criteria are:

1. Lactating females.
2. Women with child-bearing potential who are not on any medically accepted method of birth control.
3. Patients with rapid progression of their underlying which, in the opinion of the investigator, would confound the safety of adverse experience profile.
4. Patients with life expectancy less than 8 weeks,
5. Patients with neoplastic disease unrelated to breast cancer (excluding superficial skin cancer).
6. Patients with medical condition which would, in the investigator's opinion, result in the variation of absorption or metabolism of drug, i.e., ulcerative colitis, or gastrointestinal disease.
7. Patients with cardiovascular disease, diabetes mellitus, bladder disease, renal or hepatic disease, or history of alcoholism or drug abuse within the last 6 months..
8. Patients currently receiving isoniazid or being treated with allopurinol.
9. Patients unable to ingest or metabolize oral medications.
10. Patients who have taken investigational medication within 30 days prior to the start of the study.

Patients will be restricted from citrus fruit products and caffeinated beverages during blood-drawing periods and alcoholic beverages will not be allowed for 48 hours prior to, or during the study period.

All concomitant medications will continue at stable dose and reported to the investigator. Patients will be advised not to start any new medication other than the study chemotherapy regimen on days 6, 7, 13 and 14.

Patients will be randomly assigned to one of the following two treatments for 7 days and cross over to the other treatment the next 7 days (the ratio of number of patients with treatment sequence of AB:BA wil be 1:1 at each center):

Treatment A: Test drug -- Cyclophosphamide 50 mg tablets, 100 mg/m$^2$, manufactured by Roxane Laboratories, once a day for 7 days.

Treatment B: Reference drug -- Cytoxan 50 mg tablets, 100 mg/m$^2$, manufactured by Bristol-Myers Squibb, once a day for 7 days.

Patients will visit the clinic 3 times during the study, on days 1, 7, and 14. During each of these 3 days, cyclophosphamide tablets will be given with 240 mL of water under the supervision of the investigator after the time zero blood sample has been drawn and 15 minutes after a standard breakfast. During the first visit on day 1, patients will be given the medications for days 1-7.

During the second visit on day 7, patients will be given medications for days 8-14. During the second and third visits on days 7 and 14 respectively, patients will have standard breakfast before pharmacokinetic blood samplings are conducted at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, & 24 hours after cyclophosphamide dosing. They will be allowed to go home after the 12-hour blood sample draw, if preferred, and will return for the 24-hour blood sample.

After dosing on days 7 and 14, each patient will be given a diary card to record any snacks, meals or drinks consumed over the 24 hour blood sampling time. They will have medication compliance check, and will be questioned for concomitant medications and adverse experiences.

At visit 3, patients will also have physical examination, vital signs and clinical laboratory assessments. If, in the investigator's opinion, laboratory results were clinically significant at visit 3 compared to visit 1, the patient must return within 1 week of the final dose of study medication and be reassessed.

The following pharmacokinetic parameter will be computed from the cyclophosphamide concentration-time data: $AUC_{0-t}$, $AUC_{0-inf}$, $K_{el}$, $T_{1/2}$, $C_{max}$, $T_{max}$, $C_{avg}$ ($AUC_{0-t}$/24), $C_{min}$, and fluctuation [Fluct1=($C_{max}$-$C_{min}$)/$C_{min}$ and Fluc2=($C_{max}$-$C_{min}$)/$C_{avg}$].

ANOVA will be applied to the above variables and the log-transformed $AUC_{0-t}$, $AUC_{0-inf}$, $C_{max}$, and $C_{min}$. 90% confidence intervals for the ratios of the treatment means will be computed.

Comments:

1. Due to the relatively short $T_{1/2}$ of methotrexate (8 hours) and 5-FU (11 minutes), and the rapid plasma clearance of adriamycin, IV administration of these drugs on days 1 and 8 will probably have no residual effect on the cyclophosphamide pharmacokinetic parameters that will be measured on days 7 and 14.

The investigator should, however, ensure the compliance of patients with their chemotherapy regimens and no concomitant medication will affect the pharmacokinetics monitored on days 7 and 14.

2. The safety of studying this drug with the out-patients design must be considered by an institutional review board.

3. The study will be carried out at more than one clinical site, with more than one dosage levels (150 -200 mg) of cyclophosphamide, and in patients with different chemotherapy regimens (CMF or CAF). Therefore the statistical model should include factors to detect if the difference between the test and reference product depends on any of these factors, i.e., site, dose, regimen, site*treatment, dose*treatment and regimen*treatment.

   There was a statistically significant dose-by-treatment interaction in the sponsor's previous study (see attached review by the mathematical statistician on 09/16/95).

Recommendation:

The bioequivalence study protocol submitted by Roxane Laboratories, Inc. on its Cyclophosphamide 50 mg tablet compared to Cytoxan[R] 50 mg tablet, manufactured by Bristol Myers Co., is acceptable providing comments 1-3 are taken into consideration.

The above comments and recommendation should be forwarded to the firm.

/S/ 6/3/96

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG /S/ 6/3/96
FT INITIALED YCHUANG

Concur: /S/ Date: 6/3/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 40-032 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-652 (Huang, Chuang), Drug File, Division file.

First Draft, LWC, 05/21/96, c:\wpfiles\40032pr.196
Final Pink, LWC, 06/03/96, x:\new\firmsnz\roxane\ltrs&rev\40032pr.196

MAR 13 1995 MAR 13 1995

Cyclophosphamide
Tablet, 50 mg
ANDA # 40-032
Reviewer: L. Chuang
WP#40032AM.594

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
May 17, 1994
July 12, 1994

**Review of an Amendment to an In-Vivo Bioequivalence Study And Dissolution Data**

The previous submission of this application was found to be incomplete by the Division of Bioequivalence with 8 major deficiencies. The firm responded to those deficiencies in this submission as following:

1. The study is a multiple single-dose design instead of the multiple-dose design as proposed by the firm.

   The firm claimed that the protocol regimen of oral cyclophosphamide (CP) at once daily of 1-5 mg/kg was previously approved by the Agency. Moreover, the debate as to whether the study is a multiple-dose study or a multiple single-dose study has little bearing on the clinical and blood level data obtained to measure the equivalence of the two products.

   Comments:

   The reviewer can not confirm that the dosing regimen had been approved by the Agency.

2. Blood samples were drawn only at predose and during day 7, hence the results failed to demonstrate the attainment of steady state after the 7-day dosing regimen.

   The firm stated that the 144 hours and 168 hours CP concentrations indicated that these patients were at steady state and this observation is consistent with the half-life estimates obtained from these individuals.

   Comment:

   Observing the plasma concentrations at hour 0, day 7 (hour 144) and at hour 24, day 7 (hour 168), it was noted that they were within similar range ug/mL versus ug/mL). Therefore, patients may be at steady state on day 7.

3. Computation of the elimination constant (and half-life, $t_{1/2}$) of each patient during both phases of the study should be

conducted to assess changes in the elimination pattern of CP and its metabolites after multiple doses of CP. The pharmacokinetic parameter, $AUC_{0-inf}$, should be estimated and statistical analysis conducted on the resulting $AUC_{0-inf}$.

The firm replied that the patients in the study were already receiving CP as their normal therapy and any changes that might occur during repeated CP treatment should have already occurred before the study was conducted.

The firm has provided $AUC_{0-inf}$ (non-dose-adjusted) and $AUC_{0-inf}A$ (dose-adjusted) as presented below:

| Parameter | LS Means Treatment A | LS Means Treatment B | 90% Confidence Interval |
|---|---|---|---|
| $AUC_{0-inf}$ | 32.230 | 33.861 | 85.1%-102.0% |
| $LNAUC_{0-inf}$ | 3.480 | 3.548 | 86.8%-100.6% |
| $AUC_{0-inf}A$ | 35.255 | 38.254 | 83.9%-100.4% |
| $LNAUC_{0-inf}A$ | 3.525 | 3.593 | 86.8%-100.6% |

Comments:

The decrease in the $t_{1/2}$ of CP was observed in patients receiving 50 mg/kg/day for 4 days or 9.4 mg/kg/day for 5 days. No changes in $t_{1/2}$ of CP was observed in patients after 22 days on the low dose regimen, but a significant decrease in $t_{1/2}$ of CP was found in patients after receiving 100 mg/day for 6-12 months. No data are available for the dosing interval between 22 days and 6 months.

The firm did not report how long and at what dose each patient had been on the CP regimen, therefore the reviewer can not agree with the statement that 'any changes that might occur during repeated CP treatment should have already occurred before the study was conducted'.

However, judging from the small difference between the mean $t_{1/2}$ from period 1 and period 2 (5.32 hours and 5.82 hours respectively), it may be assumed that the elimination half-life did not change from period 1 to period 2.

4. The concentration of the active metabolite, phosphoramide mustard, should be measured in the study serum samples.

The firm stated that the Division of Bioequivalence communicated informally to Roxane and that

parent compound analysis was all that was needed.

The firm also stated that the literature documented that the phosphoramide mustard metabolite is an intracellular alkylating metabolite and is not in the general circulation and would not be detected by analysis.

Comments:

The reviewer can not confirm any informal communication between the firm and the Agency concerning this application.

The reviewer also can not find any supporting literature that phosphoramide mustard is not present in the general circulation.

However, it was stated in the PDR that "It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide". Therefore, the measurement of a single metabolite may not be appropriate to assess the bioequivalence of two formulations.

5. Justification of the dose-adjustment of the pharmacokinetic parameters and the conduct of statistical analysis on the log-transformed data of the non-dose-adjusted pharmacokinetic parameters.

The firm stated that there is no evidence of non-linearity across the 50-200 mg dose range.

The pharmacokinetic parameters have been re-evaluated without dose-adjustment and with log-transformation. The results are presented below:

| Parameters | LS Means Treatment A | LS Means Treatment B | 90% Confidence Interval |
|---|---|---|---|
| $LNC_{max}$ | 1.320 | 1.453 | 79.4%-96.6% |
| $LNAUC_{0-t}$ | 3.398 | 3.459 | 87.5%-101.1% |
| $LNAUC_{0-inf}$ | 3.480 | 3.548 | 86.8%-100.6% |

Comments:

Since there is no evidence of non-linearity within the 50-200 mg range, the firm's explanation for dose-adjustment is acceptable.

The 90% CI obtained without dose-adjustment were identical to those obtained with dose adjustment. This is due to the study

design and the fact the each subject received the same dose during treatment A and treatment B.

6. The appropriate statistical model used to analyze the study data should include terms for site, site-treatment interaction, dose, dose-treatment interaction, regimen and regimen-treatment interaction.

   The firm stated that there was no clear evidence of any difference in sites and did not comment on the other factors, i.e., regimen and dose.

   Comment:

   Due to the multiple sites, multiple dose and multiple regimen of the study patients, the above recommended statistical analysis should be followed.

   The Agency's in-house statistician conducted analysis and his review is attached. In summary:

   a. dose-by-treatment interaction was statistically significant ($p < .05$) for $LNC_{max}$ and maybe also for LNAUC.

   b. The $LNC_{max}$ data from the study cannot consistently establish the equivalence of the test and reference products at 200 mg dose, and it cannot establish the equivalence of test and reference products at the 50 mg, 100 mg, or 150 mg doses under any circumstances.

   c. The overall $LNC_{max}$ 90% CI, as reported by the firm, does not fall within the limits of %.

7. Clarify the limit of quantitation, which was stated to be ug/mL while samples with CP concentration of ug/mL and ug/mL were presented in the 'data tracking' section.

   The firm stated that at ug/mL, it had trouble achieving satisfactory precision and reproducibility and the limit of quantitation was then changed to ug/mL. Some sample had less than the regular volume for analysis (1 mL) and required dilution. When the dilution factor was taken into account, the concentration became ug/mL.

   Comment:

   Study samples with CP concentrations of ug/mL or ug/mL, were reported as zero in the final report. Therefore the limit of quantitation remains at ug/mL.

8. The following information was missing in the original submission:

* The demography of the study patients.

  The firm submitted the demographic infirmation of all study patients including their smoking habits, age, height, weight, and race.

* Study sequence

  Among the 24 patients whose data were used for pharmacokinetic and statistical analyses, 11 had the study sequence of AB and 13 were BA.

* Type of chemotherapy regimen

  The firm stated that each study patient was on one of the following 3 regimens: CAF, CMF or CMFVP.

  In the section of individual clinical records, out of the 24 patients, 15 were indicated to be on the CMF regimen, 5 on CAF and 4 on CMPVP.

* Clinical records

  Individual clinical records were submitted.

* Clinical study sites and number of patients at each site

  The firm submitted the following information:

| Investigator Site | Number of Patients | | |
|---|---|---|---|
| | Entered[a] | Completed[b] | Discontinued |
| | 1 | 1 | 0 |
| | 6 | 4 | 2 |
| | 9 | 7 | 2 |
| | 2 | 2 | 0 |
| | 5 | 3 | 2 |
| | 4 | 3 | 1 |
| | 8 | 7 | 1 |
| | | | |
| Total | 35 | 27 | 8 |

a = Two patients qualified, but did not enter the study.
b = Of the 27 patients that clinically completed, 24 were evaluable for bioequivalence purpose.

* The date of clinical study and the names of clinical investigators

  The dates of the study were 01/21/92 to 02/11/93. The investigators' names were listed above.

* The lot number and assay potencies of both products

  The test product was from Roxane batch #919027 which batch size was tablets. The test product's assay potency was %.

  The reference product was from Bristol Myers batch #MMCO2 and the assay potency was %

* IRB approval letter and patient's informed consent form

  The protocol dated 05/06/91 and amended 08/28/91 was

approved by the on 01/21/92.

The patient's informed form was approved by the same board on 04/14/92.

* Reasons for the dropout of 8 patients and the status of "no samples received for assay" for subject #13.

  The firm reported that 2 patients dropped out due to adverse experiences (nausea, acute cholecystitis, cholelithiasis, large gall bladder, vomiting, edema and weakness), one due to illness that was unrelated to study drug, one died and another withdrew prior to study entry, one failed to comply with study medication schedule, one failed to give day 14 blood draw and one dropped with no known reason.

  The firm did not explain the status of "no samples received for assay" status of subject #13.

Comment:

The information submitted by the firm is acceptable except the last item where the firm did not explain the status of "no samples received for assay" for subject #13.

In addition to the 8 deficiencies discussed above, a deficiency in the in vitro dissolution testing was overlooked in the previous review. The firm employed USP XXII apparatus 2, paddle, at 50 rpm while the agency specifications requires the use of USP XXII apparatus 1, basket, at 100 rpm.

Deficiencies:

1. The overall $LNC_{max}$ 90% CI, as reported by the firm, does not fall within the limits of %.

2. The presence of significant dose-by-treatment interaction for $LNC_{max}$ raises concerns that test and reference products might be equivalent for some doses, but not for others.

3. The $LNC_{max}$ data cannot establish the equivalence of test and reference products at the 50 mg, 100 mg, or 150 mg doses under any circumstances and also fails to consistently do so at 200 mg.

4. The firm should explain the status of "no samples received for assay" status of subject #13.

5. The firm should conduct comparative dissolution testing on same lots of both test and reference products used in the bioequivalence study. The dissolution testing should be conducted in 900 mL of deaerated water, at 37° using USP XXII apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

> Not less than % of the labeled amount of cyclophosphamide in the dosage form are dissolved in 45 minutes.

Recommendation:

1. The bioequivalence study conducted by Roxane Laboratories, Inc. on its Cyclophosphamide 50 mg tablet compared to Cytoxan® 50 mg tablet, manufactured by Bristol Myers Co., has been found unacceptable by the Division of Bioequivalence due to deficiencies #1-4 stated above.

2. The dissolution testing data conducted by Roxane Laboratories, Inc. on its Cyclophosphamide tablet, Lot 919027, manufactured by Bristol Myers Co., is not acceptable due to deficiency #5.

The above comments, deficiencies and recommendation should be forwarded to the firm.

/S/

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED AJACKSON /S/
FT INITIALED AJACKSON

Concur: /S/ Date: 3/13/95
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

3.1

MAR 15 1995

Cyclophosphamide
Tablet, 50 mg
ANDA # 40-032
Reviewer: L. Chuang

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
January 5, 1995
January 13, 1995

**Review of an Amendment to an In-Vivo Bioequivalence Study And Dissolution Data**

This is a unsolicited amendment to a pending ANDA.

The firm reassessed the data for the bioequivalence study in breast cancer patients and found that subject #8 is the only patient in the study who had a concomitant cancer, the von Reklinhausen's disease which is characterized by cutaneous and internal tumors associated with central and peripheral nervous system. It is estimated that up to 25% of patients with von Recklinghausen's disease have gastrointestinal involvement resulting in disordered gut mobility, gastrointestinal stromal tumors, endocrine cell tumors of the duodenum and perampullary region, and other gastrointestinal tumors.

The firm claimed that this concomitant cancer could have resulted in intraindividual variation of the absorption of cyclophosphamide due to the disease's pathology.

The firm conducted statistical analysis excluding subject #8. The results with and without subject 8 presented below indicated that the 90% confidence interval of $LNC_{max}A$ fell within the acceptable range:

| Parameter | LS means Treatment A (Roxane) | LS Means Treatment B (Bristol Myers) | 90% Confidence Interval |
|---|---|---|---|
| AUCA* (include #8) | 32.346 | 34.618 | 85.8 -- 101.1 |
| AUCA* (exclude #8) | 32.514 | 34.282 | 87.3 -- 102.4 |
| LNAUCA* (include #8) | 3.443 | 3.504 | 87.5 -- 101.1 |
| LNAUCA* (exclude #8) | 3.447 | 3.493 | 89.1 -- 102.4 |
| $C_{max}A^*$ (include #8) | 4.030 | 4.649 | 77.7 -- 95.6 |
| $C_{max}A^*$ (exclude #8) | 4.102 | 4.648 | 79.4 -- 97.1 |
| $LNC_{max}A^*$ (include #8) | 1.366 | 1.498 | **79.4 -- 96.6** |
| $LNC_{max}A^*$ (exclude #8) | 1.388 | 1.496 | **82.1 -- 98.3** |

* = Dose-Adjusted

Comments:

1. Although subject #8 had a concomitant cancer, there are no documented test results on the subject that her gut gastrointestinal function was affected.

2. By excluding subject #8, who took 100 mg dose regimen during the study, the $LNC_{max}$ data from the study still cannot consistently establish the equivalence of the test and reference product at the 200 mg dose, and still cannot establish the equivalence of the test and reference product at 50 mg and 150 mg doses under any circumstances.

3. The dose-by-treatment interaction remains significant after excluding subject #8.

Recommendation:

The previous recommendation that the study has been found unacceptable remains unchanged.

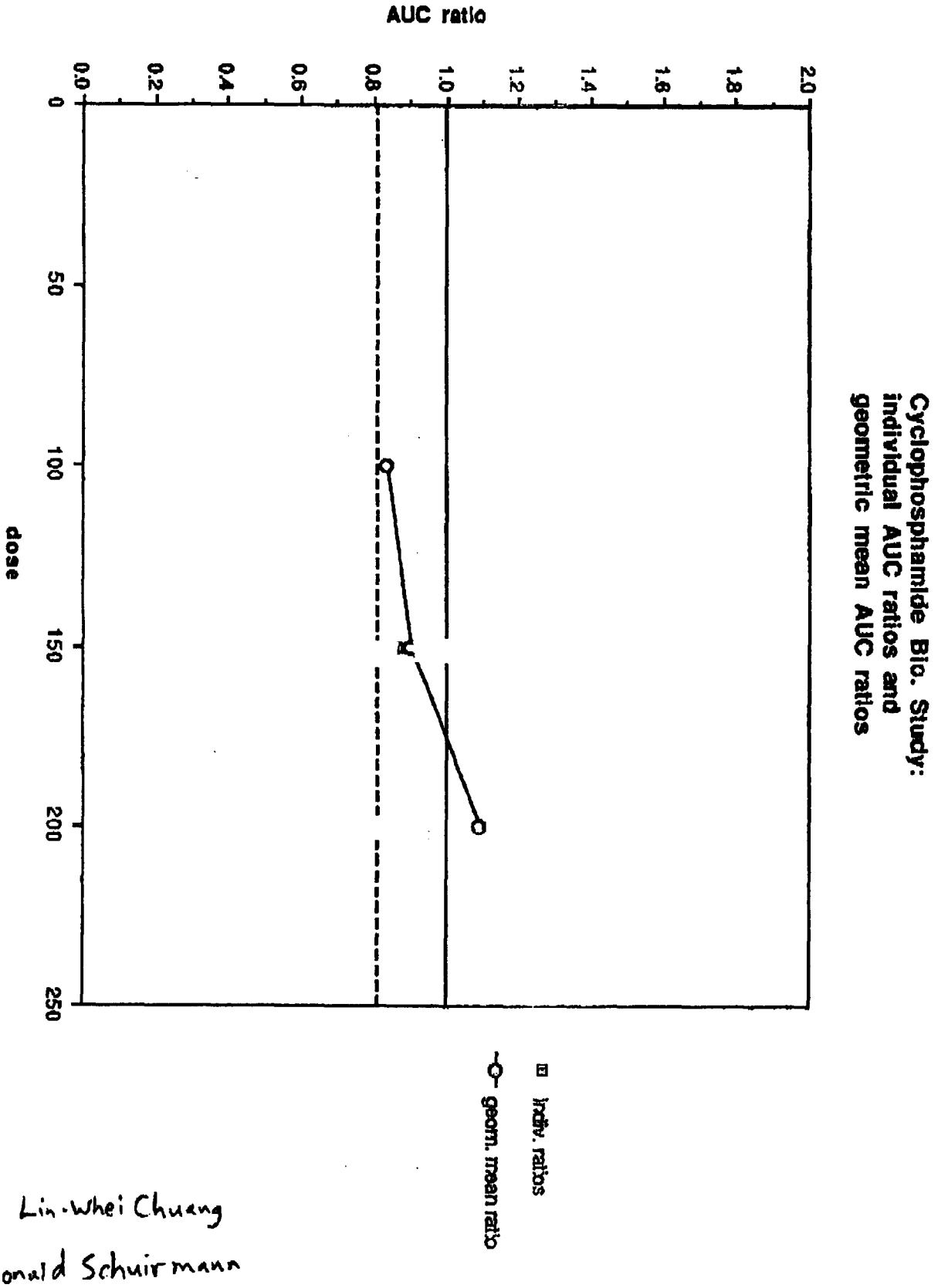
/S/

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/

Concur: /S/ Date: 3/15/95
Rabindra Patnaik, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 40-032 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-652 (Wu, Chuang), Drug File, Division file.




Graph for Lin-Whei Chuang
from Donald Schuirmann

FEB 26 1992

**CYCLOPHOSPHAMIDE**
TABLET 50 mg
ANDA # 40-032
Reviewer: Gur J. P. Singh
File # 40032PD.N91

**ROXANE LABORATORIES**
P.O. Box 16532
Columbus, Ohio.
Submission Date:
November 26, 1991

***REVIEW OF A BIOEQUIVALENCE STUDY PROTOCOL AND DISSOLUTION DATA***

This firm has submitted *in vitro* dissolution data and a protocol for bioequivalence study on its cyclophosphamide 50 mg tablet.

**PROTOCOL (#12427)**

A bioequivalence study comparing Roxane's cyclophosphamide 50 mg tablet with the reference product, Cytoxan$^{R}$ 50 mg tablet manufactured by Mead Johnson, has been initiated at (pp 19). The firm expects to submit the results of this study soon. Therefore the review of this protocol will not be done at this time.

***IN VITRO* DISSOLUTION TESTING**

| | |
|---|---|
| METHOD: | USP XXII |
| APPARATUS: | 2, Paddle |
| SPEED: | 50 rpm |
| MEDIUM: | 500 mL $H_2O$ |
| NUMBER OF TABLETS TESTED: | 12 |
| SAMPLING TIMES: | 15, 30, 45 and 60 min. |

FDA SPECIFICATIONS: NTL %, 45 min, 900 mL $H_2O$ (deaerated), USP XXII Basket, 100 rpm.

The method employed by the firm for *in vitro* dissolution testing does not meet the agency specifications. The agency requires the use of USP XXII apparatus I, Basket. Instead, the firm has employed USP XXII apparatus 2, Paddle. Therefore the *in vitro* dissolution testing conducted by this firm on its cyclophosphamide 50 mg tablet is not acceptable, and the review of the dissolution data is unnecessary.

**COMMENTS**

1. The review of the protocol (#12427) will not be done at this time since the bioequivalence study is already in progress.

2. The *in vitro* dissolution testing conducted by this firm does not meet agency specifications, and therefore not acceptable.

**RECOMMENDATIONS**

1. The *in vivo* bioequivalence study on cyclophosphamide, 50 mg tablet, manufactured by Roxane Laboratories for which this protocol was submitted has already been started. The Division of Bioequivalence, therefore, will not review the protocol. We look forward to reviewing the study data when it is submitted to the agency.

2. The *in vitro* dissolution testing conducted by Roxane Laboratories on its cyclophosphamide tablet, 50 mg, lot #919027, is not acceptable. The dissolution testing should be conducted in 900 mL of deaerated water using USP XXII apparatus I (Basket) at 100 rpm . The test drug should meet the following specifications:

   Not less than % of the labelled amount of drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of above recommendations.

Gur J.P. Singh, Ph.D.
Division of Bioequivalence
Review Branch II.

/S/

RD INITIALLED RPATNAIK
FT INITIALLED RPATNAIK

/S/

GJPSINGH/02-14-92/40032PD.N9

CC ANDA # 40032, original, HFC-130 (JALLEN), HFD-604 (Hare), HFD-655 (Pelsor, Singh), Drug File.